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MERCK
Research Laboratories

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Guidance for Industry on
Computer Systems Used in Clinical Trials
Docket # 97D-0228

Merck & Co., Inc., is a worldwide research-intensive company that leads the ethical U.S. pharmaceutical industry in discovery, development, production and marketing of human health products.. Merck Research Laboratories (MRL), Merck's research division, is one of the leading biomedical research organizations dedicated to improving human health.. Through a complex multidisciplinary process, MRL involves scientists from every technical discipline in targeting, discovering, and testing compounds to conquer today's unique diseases. MRL's innovation strategy includes research and development of many compounds or potential drug candidates at one time. The MRL R&D process for human drugs can be separated into three main stages; basic research, followed by developmental research and, finally, human clinical research.

Merck currently has many new compounds in clinical development and additional indications are being explored for approved drugs. Merck conducts clinical trials in many countries throughout the world. Commercialization of products in many countries directly depends upon regulatory climates that foster timely development and government policies that are consistent and socially responsible, but do not add extra uncertainty or cause unnecessary delay to the research process.

For these reasons, we are very interested in and well qualified to comment on this FDA Guidance which identifies issues pertaining to computer systems used to generate, collect, maintain, and transmit clinical data intended for submissions to the FDA. Merck & Co., Inc. has previously provided comments to the *draft* FDA Guidance on 19 August, 1997 (Larry Bell to FDA). Reference is also made to a visit by Mr. Gregory Brolund, FDA, to Merck & Co., Inc. on 6 May 1999 to discuss how Merck & Co., Inc. is responding to and our concerns about 21 CFR Part 11. The purposes of this letter are to expand on several of our previous comments and to raise additional concerns.

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This Guidance provides laudable plans to achieve control and safeguards for data entry, security and independently generated audit trails. While we continue to agree with many of the recommendations given in the Guidance, we offer the following comments and recommendations (given in italics) for your consideration.

In addition, it must again be stressed that for computer systems currently in use for clinical trials, the technology and methodology are not currently in place or even available [for full remediation] to comply to *21 CFR Part 11*. In such cases, the development and validation of adequate ways to quantify existing systems may be considered too costly to assure compliance to the requirements of *21 CFR Part 11*. In other cases, new software that would be compliant to *21 CFR Part 11* is not readily available. If we waited for that software to become available, a significant and unjustifiable delay would be encountered for the start of important new clinical studies.

Overall Comments about the Guidance

We understand that most of the changes covered by the Guidance are within the stated intent of *21 CFR Part 11*, which would encompass all computer systems currently for use by industry in clinical trials, as well as those yet to be developed. We acknowledge that reliance on electronic signatures and records will steadily increase and Merck & Co., Inc. is committed to ensuring the integrity and quality of our data. But, it is believed that because of the lack of *21 CFR Part 11*-compliant vendor-provided systems for clinical or for other uses, transition and scaling to global systems to handle clinical data will take many years.

While it has been stated by FDA in a number of public meetings that over 500 comments have been provided by industry about the draft Guidance, it is clear that the final Guidance has not been significantly changed based on those comments and in fact, has been further complicated by the addition of a troubling section entitled **VI. SYSTEM FEATURES D. Reconstruction of Study** referred to in detail below.

Further confusion in regard to the relationship of *21 CFR Part 11* regulations and the Guidance is evident in light of the FDA's recent effort (May, 1999) to solicit input from several major pharmaceutical companies, including Merck & Co., Inc. about the difficulties they are experiencing with complying to *21 CFR Part 11* regulations. It seems incongruous that the Guidance, with even more stringent requirements than *21 CFR Part 11*, was issued *before* an internal FDA assessment of industry's difficulties with *21 CFR Part 11* was completed. Further, the compliance aspect of *21 CFR Part 11* continues to be emphasized in a number of FDA-sponsored meetings or in meetings in which FDA has been an active participant (e.g., FDA-sponsored live video workshop on *21 CFR Part 11* [Jan. 1999], Society of Quality Assurance meeting [1Q99], DIA Workshop on Computer Validation [April, 1999]) .

In certain circumstances, it is not unreasonable for a firm to maintain a "legacy" computer system for five to 10 years, *without* upgrading for *21 CFR Part 11* requirements. This

assumes that the legacy system is validated and the justification for not upgrading is documented and the system retirement is executed as planned without adding additional studies to the noncompliant system. One example would be a clinical system containing data from a long term trial where the risk of modifying the system outweighs the benefit of upgrading.

The following discussion briefly summarizes the key issues from our review of the Guidance. A detailed list of comments (with reference to lines, section or subsection) is also provided. Comments have been grouped as major or recommended clarification through changes in wording.

Comments on specific sections of the Guidance:

II. DEFINITIONS

Major Comments
Line 5 – This definition of "certified copy" needs to be clarified. What is meant by the term "exact"? Does this mean that the "certified copy" must be kept on exactly the same media? Does it mean that a "certified copy" of an electronic record must also be an electronic record?

Recommendation: We suggest deleting the word "exact" or changing it to be "accurate and true".

III. GENERAL PRINCIPLES

Major Comments
A. The clinical protocol is meant to inform clinical investigators of the key elements to properly conduct the study. It is not meant to contain detailed specific information about computer systems. It is our position that the study protocol should only identify the *major* processes that are to be computerized to collect patient data. Therefore, including a statement such as "Patient evaluations can be entered directly into the laptop computer by the Investigator and/or study staff" is an adequate level of detail to include in the protocol. It is unnecessary and in some cases not possible to identify all details about computer systems at the time the protocol is drafted. Merck's technical documentation, in support of each protocol, however, does contain this information. The data entry model may vary by protocol and within a protocol.

C. In some cases, source documents, by themselves, may not be enough to reconstruct the trial. Additional supporting documentation from the sponsor may be needed to provide full understanding of the software/hardware used in the trial.

F. Line 17. As previously commented, the definition of "certified copy" needs to be clarified to identify that true and complete signed printouts of electronic records are acceptable at the investigator site.

G. Many vendor systems today do not meet the requirement of "should not obscure the original information".

H. Line 24 . As stated in our previous response to the draft Guidance, the Guidance states that for changes to data made at the research site, the clinical investigator's documentation should include who made the changes, and when, how and ***why*** they were made. This recommendation adds additional regulations *beyond* what is currently required by *21 CFR Part 11* and the original regulations. Specifically, current changes to a "paper" document do not require documentation of "why" the change was made.
21 CFR Part 11 further stated in the preamble that "why" was not required for audit trails because it might be "more expensive to implement". In addition, the complexity of adding a reason for every change would unnecessarily enlarge and complicate the audit database, without any apparent added value. The audit trail should therefore *not* include the reason for change except in unusual circumstances. This is consistent with current Good Clinical Practice expectations. Noting the reason for all changes would obscure the audit trail with unnecessary details, since many changes are simple corrections of typographical errors. In addition, many of the "changes" on the electronic audit trail are simply reflective of changes/corrections to the original source documents. Finally, many vendor systems do not currently meet the "audit trail" requirement in accordance with *21 CFR Part 11.10.10(e).*

Continued Recommendation: Elimination of the recommendation to include "why" changes were made to the electronic record and which computerized systems are used for generation, collection and transmission of data should again be considered because of the enormous extension of the audit trail database that it would entail for no significant gain and because its capture is not specified in 21 CFR Part 11. The last sentence in this section should therefore read: "Documentation should include who made the changes, when, and what was changed."

V. DATA ENTRY

A. Electronic Signatures

Major Comments
Section 1. Line 12 – Display of a person's printed name throughout the data entry session is not well defined. This section also suggests that every time a piece of data is added to an electronic record an electronic signature is required. This differs from *21 CFR Part 11* where the electronic signature is *only* required where a traditional handwritten signature is required. Displaying the full name of the data entry person throughout the data entry session is not necessary in many data entry scenarios. When a terminal or PC is dedicated to an individual, there is little chance of someone else mistakenly entering data on that machine.

Recommendation: We suggest the term "data entry screen" be replaced with "data entry screen where a person's electronic signature is being applied".

Section 2. Access to data entry screens is password protected and should be representative of the person logged onto the system using that password. The automatic screen saver using a password should protect violation by unauthorized users.

Section 2a. Display of the person entering the data on every screen is problematic and does not increase the value of the electronic record. Display of the name on each screen is not always possible with some vendor-provided software.

Section 4. There is no ability to age passwords with some vendor-provided software.

B. Audit Trails

Major Comments
Section 1a. The phrase "when it is saved to a durable media," should be deleted.

Recommendation: Add a second sentence that reads "The audit trail can be a single secured audit trail file created and maintained by the application, multiple secured audit trail files created by copying the audit trail from the application or a computer-generated printed audit trail report."

Section 1b. Technology to support audit trails for long periods of time may not be available. This is particularly relevant in long term clinical trials lasting several years.

Section 3. What is meant by a certified copy? In one of our systems, investigators retain and sign the hard copy Case Report Form produced from the database that contains the results of all audited transactions. Electronic audit trails are not retained at the site as the hard drives are returned to the sponsor. A printout of the audit trail report could be provided to the site.

C. Date/Time Stamps

Major Comments
We agree with the position expressed in the Guidance document that controls should be in place to ensure that system's date and time are correct and that the date and time are not changed by unauthorized means. We also agree with the proposed outcome that dates and times should be local to the activity being documented. However, the means by which this is accomplished should be left up to the discretion of the individual sponsor(s). Mandating the use of local time can create inconsistencies for global systems and confounds time sequencing integrity. When collectors are built, they are usually set up with the local time that pertains to that of the clinical investigator or Merck person who will actually use them at the site. However, if data are entered *directly* into a central database at a Merck subsidiary, the date and time of entry are taken from the system at

that location, regardless of the location and local time of the investigator from which the data are derived.

Line 6 – In the *21 CFR Part 11* preamble, the use of local time is a *suggestion*. In the Guidance it is now stated as an *absolute*.

Recommendation: We suggest this sentence be changed to "Dates and times stored in electronic records are to be displayed as local time or the displayed time should be easily converted to local time. Algorithms that are necessary to convert a displayed time to local time must be documented. Date and times are to include year, month, day, hour, and minutes."

VI. SYSTEM FEATURES

B. Facilitating the inspection and review of data

Major Comments
Merck does not have "*data tags*" to indicate data that has been changed at this time.
Flagging changes or deletions from the audit trail in color has little value to data entry personnel.

Recommendation: Line 13, second sentence should be deleted in that it specifies a design approach.

C. Retrieval of Data

Major Comments
Line 7. "computational methods used to derive data" - This statement needs to be qualified as this would refer to any programming done by statistics or data coordination would require this level of retrieval. In addition, when we migrate from one system to another, at least for legacy systems, we do not even have a full or partial audit trail to migrate.

Recommendation: This section should be clarified to limit the need to retrieve all computational methods and acknowledge that audit trails from legacy systems may not exist.

D. Reconstruction of Study

Major Comments
Line 1. This paragraph defines the method by which the FDA expects to be able to recreate a study, i.e. using exactly the same analysis tools used in the original study.
Our processes for obtaining and managing data are documented in SOPs. These SOPs cover processes including change management, systems development and data management. Product and system change orders track changes made to software products

and system changes. We maintain versions of software for review, but since we validate every release of software and hardware for compatibility with the data, we do not try to recreate a previous environment totally. In fact we question the need for this total reconstruction and its feasibility from a practical standpoint. From a realistic standpoint, for collectors alone we could end up with one hard drive per 20 patients for up to 40,000 patients per year.

In addition, it is unreasonable to expect that a company could retain the exact software versions and hardware used in a particular system, particularly for long term studies lasting many years.

Recommendation: Everything after the first two sentences should be deleted. As long as the analysis methods are adequately documented, this should be acceptable. Since FDA representatives have stated that the method described in the Guidance would be one possible option in rare circumstances, its presence in the Guidance is misleading. The need to retain all software versions for a system would only be necessary in rare circumstances where data are suspect and/or transformations could not be traced through study documents or the audit trail.

VIII. SYSTEM DEPENDABILITY

A. Systems documentation

Major Comments
We agree that the FDA has the right and should inspect documentation, possessed by a regulated company that demonstrates validation of software. We also agree that documentation that provides an overall description of computerized operations and the relationship of hardware, software, and physical environment should be available at the site as appropriate. However, it is generally not practical to keep documentation that demonstrates validation of software at clinical sites. Duplicate copies of the systems documentation would be difficult to control and we would be disclosing our system designs in an unprotected environment. Therefore, this confidential information must be maintained at corporate headquarters. Information needed by FDA inspectors to adequately perform their audit could be sent to the sites prior to the inspection.

Recommendation: It should be recognized that in some cases it may be problematic to provide all validation documentation to a site that is being inspected. Study sponsors should be responsible for ensuring that documentation demonstrating validation of software be available if the sponsor was responsible for providing such software to the investigator for the purpose of conducting the clinical trial, and that it be kept with the sponsor. Often the system used at the site is only one component of a large, complex base system. The validation of the entire system may consist of hundreds of binders of information and it would not be appropriate for the site to have this information. It would, however, be appropriate to have an overview and an index of this documentation available at the site.

C. Change Control

Major Comments
Line 5 – second paragraph – The term "revalidation" is not meaningful for a system that was developed and is maintained using a system life cycle methodology. As part of an SLC methodology, after system implementation, assurances of operations are maintained through performance observation and change control as documented in Standard Operating Procedures.

Recommendation: This paragraph should be deleted.

XI. RECORDS INSPECTION

Section B.

Major Comments
The sponsor should provide the hardware and software to review the electronic records at the site or retain paper-based certified copies.

Recommendation: We propose to permit paper based "certified copies" to be present at the site that could be inspected in lieu of electronic records.

We appreciate the opportunity to further comment on this Guidance and request an opportunity to discuss in greater detail with IT, Regulatory and Compliance FDA personnel our continuing concerns about these initiatives. While we are in agreement as to the direction that these Regulations/Guidance are headed, implementation of them by industry and compliance to them as assessed by FDA must follow a logical and appropriate course that is both technically possible and reasonable.

Very truly yours,

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/ufda/guidance

cc: Gregory Brolund
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